COOLING PROCESSES AND CONGEALING

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INTRODUCTION

The purpose of this article is to introduce the major concepts and applications of cooling and congealing processes in the pharmaceutical industry. A cooling and congealing process must follow any process involving a melt. The melt-congealing technique has been practiced in the manufacture of wax-based suppositories for over 100 years. New applications have evolved quickly in the last 40 years to meet the increasing need for improving the solubility and consequent bioavailability of poorly water-soluble drugs and making modified-release drug products. Solid dispersions, matrix tablets, and coated drug-laden beads are some common examples. One of the methods of preparing solid dispersions is melt-congealing. The basic concept and process required to form solid dispersions of poorly water-soluble drugs in solid matrices is attributable to the work of Sekiguchi and Obi in 1961 (1). They melted a sulphathiazole–urea mixture of eutectic composition at above its eutectic temperature, solidified the dispersion in an ice bath, and pulverized it into a powder. A modification of the process involves spray-congealing from a modified spray-dryer onto coated metal surfaces and has been used for dispersions containing mannitol (2). Hot-melt coating and granulation processes have also been used in the development of wax-coated or wax-based matrix sustained-release products.

In this article, typical systems that make use of melt-congealing processes, the equipment and important operating variables used, typical matrix substrate materials, important processing considerations, and the advantages and disadvantages of using these systems are addressed.

PRINCIPAL CONCEPTS

Many review articles and many more research studies have been written on the use of systems involving the congealing and cooling of solid mixtures or solutions to produce both fast-release and sustained-release dosage forms. There are many reasons for using such systems. An overview of the uses of congealed solids in the production of pharmaceutical dosage forms is shown in Fig. 1. From this figure we can see that the congealable solid may play an active role in controlling the rate of release of the active ingredient or may just be a cosmetic agent.

When the role of the congealable solid is to retard the rate at which drug is released, the congealed solid may be used as an overcoat on a substrate containing the active (e.g., a drug-laden nonpareil). In this case, typical coating equipment such as fluidized beds and perforated pans can be used. Alternatively, the congealable solid may be part of a drug-containing matrix that is permeable to gastric fluids or is erodable. In this case, the dosage form may be produced using a variety of methods, e.g., spray-congealing of a liquid (melt), granulation using a high-shear granulator, extrusion using a twin screw extruder, etc.

When the object is to increase the rate of drug dissolution, the drug is usually dispersed in a matrix composed of the congealable solid. The first step in this process is to form a solution or well-mixed dispersion of drug in the molten carrier. Subsequently, this mixture is cooled and solidified, and the resulting solid forms a solid matrix in which drug is very finely dispersed. This method can yield a solid dispersion in which the drug is dispersed at a molecular level, and the rate of dissolution of even very poorly soluble drugs can be enhanced significantly owing to the increase in exposed drug surface area. Spray-congealing and melt-granulation processes are often used to produce this type of product.

The use of a congealable solid as a taste-masking agent or for cosmetic purposes is also reported in the literature. Cosmetic uses usually involve a coating process, whereas taste-masking can be implemented using both overcoating and drug–carrier matrix formation.

Formation of Dispersions of Drugs in Carriers

One important reason for forming a drug dispersion in a carrier is to increase solubility of poorly water-soluble

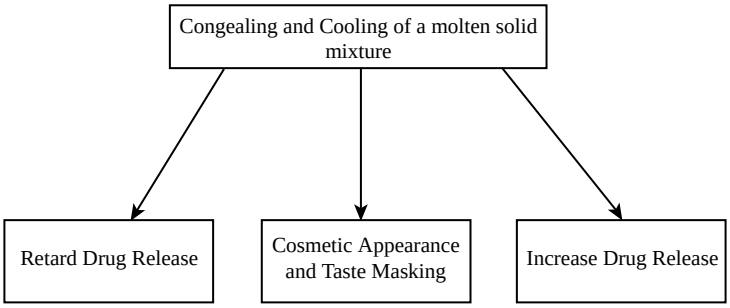

Fig. 1 General overview of uses of congealed solids in pharmaceutical dosage forms.

drugs. The dispersion of the active ingredient in a suitable matrix or carrier provides a large, exposed, drug surface area that compensates for the poor water solubility of the drug. In principle, a large surface area can be provided by fine milling (micronization) of the drug and subsequent dispersion of the drug powder in a carrier. However, owing to the cohesive nature of very fine particles, the effective dispersion of the micronized drug into the carrier can be problematic, resulting in maldistribution of the drug and consequent poor release characteristics. Despite this disadvantage, the rapid cooling and "freezing" of liquid carriers containing dispersions or slurries of fine drug powder are practiced, as is the melt granulation of a drug with a molten substrate. Another approach is to dissolve the drug into a liquid carrier and then to rapidly cool and congeal the mixture. The resulting solid will contain drug particles dispersed at the molecular or near molecular level within the solidified matrix carrier. Clearly, for this process to be effective, it is preferable that the drug is soluble in the molten carrier. A significant increase in drug-dissolution rate can then be achieved. It should be pointed out that the properties of both the drug and carrier, their interactions, the rate of cooling and congealing, and the conditions of storing the final dosage form all play an important role in the performance of the final product. All these factors are addressed in the sections below. The phase diagrams describing the behavior of different binary drug–carrier systems are reviewed in the following section.

Phase Diagrams

As an example of a liquid–solid phase diagram, we consider the salol–thymol system shown in Fig. 2 (3). This system represents a simple eutectic in which the two components are totally miscible in the liquid phase and totally immiscible in the solid phase. From Fig. 2, we see that the diagram is divided into four zones. In zone 1, both components exist as a liquid solution; in zones 2 and 3, both components exist as a liquid solution in equilibrium with the other component in the solid form. In zone 4, both components exist as solids. Each zone boundary represents an equilibrium line. For example, consider a salol–thymol system containing 64 wt% thymol at a temperature of 48°C. This is denoted by point A on the diagram. If we slowly cool this solution (at constant pressure), then at approximately 30°C (point B) we will see that the first crystal of pure, solid thymol forms. If we cool the mixture more, pure thymol will continue to crystallize, and the resulting liquid solution becomes depleted of thymol. At approximately 20°C, we are at point C, and the resulting solution, which is in equilibrium with pure thymol (point D), has a composition of 48 wt% thymol, shown by point E. Continued cooling brings us to point F, where the solution composition is shown by point G. This is the eutectic composition. Further cooling beyond point G to point H, for example, gives rise to the formation of two solid phases, namely, pure salol (point I) and pure thymol

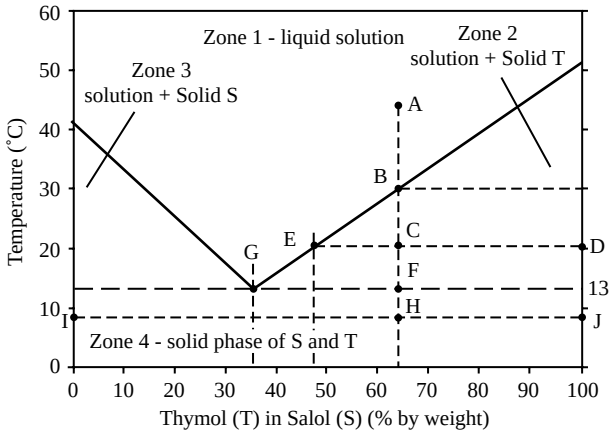

Fig. 2 Phase diagram for the thymol–salol system. (From Ref. 30.)

(point J). If we were to repeat this cooling process but start with a liquid solution with a composition to the left of the eutectic point (G), then the phase transformations would be similar except that pure salol would crystallize, and the remaining solution would become depleted in salol. The composition of this solution would move to the right and would eventually reach the eutectic composition G when the temperature reached 13°C. Further cooling would produce two solid phases of pure salol and pure thymol. The eutectic point (G) is the only condition at which a liquid solution of salol and thymol is in equilibrium with both pure solid thymol and pure solid salol. Recalling the Gibbs phase rule for systems in equilibrium:

$$F = 2 + C - P \tag{1}$$

For our salol–thymol system at the eutectic, we have three phases ($P = 3$) and two components ($C = 2$); therefore, we have only one degree of freedom ($F = 1$). For the system considered in Fig. 2, the pressure of the system is fixed, thus accounting for the single degree of freedom. Therefore, for such a system at a known pressure, there only exists a single temperature at which the eutectic can form, which is 13°C for this case.

The salol–thymol system presented is an example of a system that yields a solid dispersion when a solution is cooled rapidly. This solid dispersion consists of an intimate crystalline dispersion or mixture of one component distributed in the other. The uniformity of the dispersion of the two solid phases in each other is important to the dissolution behavior of the system. With all other factors being equal, the more uniform the dispersion, the faster and more reproducible will be the dissolution. It should be noted that the information given in Fig. 2 is accurate only if the system is in equilibrium. The conditions prevailing in any production process will most often fall short of providing equilibrium. Indeed, the idea of rapidly cooling a solution will inevitably lead to temperature and concentration gradients within the liquid and result in significantly different local congealing rates. The cooling and thickening (increase in viscosity) of the liquid act to trap crystals within the matrix and tend to minimize the diffusion and migration within the matrix. This has an added effect of limiting aggregation of the crystals and maintaining the drug in a well-dispersed form. Therefore, it can be seen that the design of the congealing device or equipment is of significant importance in the production of well-controlled dosage forms utilizing this technology. From Fig. 2, it is clear that rapid cooling of a solution with the eutectic composition can give rise to a well-dispersed solid dispersion and requires the least amount of cooling duty. However, the drug-loading in the final dosage form, along with other factors, often precludes the congealing of eutectic mixtures in favor of other liquid compositions. Solid dispersions that exhibit negligible mutual solubility in the solid phase giving rise to eutectic mixtures, as previously described, are uncommon. Examples are given by Ford (4) and include paracetamol-urea, by Goldberg et al. (5), griseofulvin–succinic acid, by Goldberg et al. (6), and griseofulvin–PEG 4000 and 6000, by Chiou (7).

Another form of solid dispersion is the solid solution. The phase diagram for two materials (X and Y) that give rise to solid solutions is different from that previously discussed; an example of such a system is shown in Fig. 3 (8). This diagram is an example of a system in which both components (drug and carrier) have a limited solubility in each other in the solid phase. Consider the cooling of a liquid with composition and temperature given by point A. As the liquid is cooled, it will reach a point B on the equilibrium line. At this point, the first crystal of solid phase will be formed. The composition of this solid phase (α) is given by point C, and comprises a solid mixture of both X and Y. The composition of the liquid in equilibrium with this solid is given by point B. As the cooling continues, more solid will crystallize out of the solution, and the compositions of both the liquid solution and the solid change during this process. At point D, the eutectic temperature is reached. Cooling below the eutectic temperature causes two solid phases to crystallize from solution. The compositions of the two phases are given by the endpoints of the constant temperature line (points E and F); these two solid phases are in equilibrium with the remaining eutectic solution. Just as in the simple system illustrated in Fig. 2, there is a single eutectic

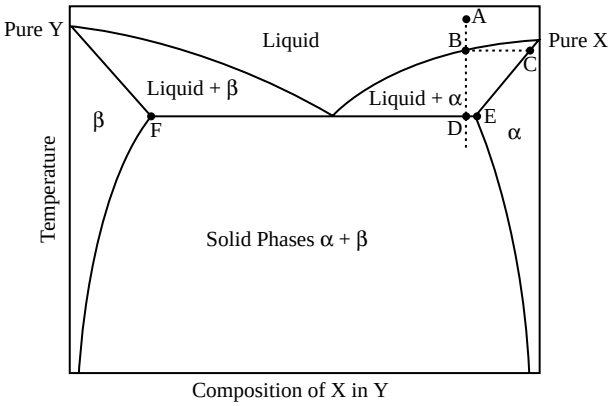

Fig. 3 Phase diagram for two components, X and Y, which are miscible in the liquid phase and mutually soluble in the solid phase. (From Ref. 8.)

temperature at which liquid and both solid phases can coexist. However, unlike the simple system, the composition of the solid phases will change with temperature.

Other structures may exist owing to interactions between the drug and carriers. Ford (4) addresses the following systems: glass solutions and glass suspensions, amorphous precipitations in a crystalline carrier, compound or complex formation, and combinations of these systems.

COMMON CARRIERS/EXCIPIENTS

Desirable Properties of Carriers

The properties of the congealed carriers clearly control the release of the drug from the dosage form. Reviews by Ford (4) and Achanta and associates (9) have been carried out in which the carrier properties are compared and contrasted, and these are summarized here. For hot-melt coatings, Achanta and associates (9) give the following ideal coating material characteristics:

1. It should be stable below 200°C.
2. It should have a melting point in the range of 75–80°C.
3. It should possess a narrow melting-point range and should not undergo softening before melting.
4. Its thermal behavior in the range of 30–200°C should be independent of its thermal history, method of preparation, and method of storage.
5. No crystal modifications should occur when it is exposed to temperatures up to 200°C.
6. It should be stable when subjected to thermal cycling.
7. It should possess a low melt viscosity to facilitate flow and spray formation.

These characteristics essentially ensure that the coating material is stable under typical coating conditions (items 4–6), that unwanted agglomeration is minimized (item 3); that it can be easily sprayed (item 7); and that operating temperatures are moderate so as to minimize drug degradation (items 1 and 2). In addition to these attributes, the coating material should clearly not interact with or adversely affect the drug's bioavailability.

For the formation of solid dispersions by congealing a melt of poorly water-soluble drug and carrier, Ford (4) recommends the following "ideal" characteristics for the substrate/carrier material:

1. It should be freely water soluble with intrinsic rapid dissolution properties
2. It should be nontoxic.
3. It should be chemically, physically, and thermally stable, with a low melting point. On solidification, it should crystallize rapidly and maintain the drug as a fine crystalline dispersion. The carrier and drug should be miscible in the liquid to avoid irregular crystallization and subsequent variability in dissolution rate.
4. The carrier should ideally increase the water solubility of the drug.
5. The carrier should not form stable complexes with the drug that would retard dissolution.
6. The carrier should be pharmacologically inert.

These characteristics ensure that, on solidification, the drug will be well dispersed with a large surface area available for dissolution (item 3); that the carrier will not inhibit the dissolution process or effect the drug (items 1, and 3–5); and that the carrier is inert (items 1 and 6). Above all, all of the carriers/excipients should have necessary regulatory approval for pharmaceutical use.

The carriers used in the production of sustained-release matrix tablets of water-soluble drugs by melt-congealing share some of the characteristics of carriers used for hot-melt coating and solid dispersion preparations. However, most of them have melting points in the range of 50–85°C.

Suitable Commercial Excipients

In general, an ideal carrier or coating material will not be available, and some compromises will have to be made. Perhaps some of the most important and common problems associated with the use of these carriers are their tendency to form crystalline polymorphs during the congealing process. In addition, there are subsequent changes in dissolution characteristics that occur on storage caused by changes in crystalline structure. The problems of changes in crystallinity are addressed later.

Congealed solids commonly used as carriers and coating materials have been summarized by Ford (4) and Achanta (9) and are:

Citric and Succinic Acids: Citric acid was used in solid dispersion preparations because of its high water solubility and its capability of glass formation. The monohydrate melts at approximately 100°C, whereas the anhydrous form melts at approximately 153°C. Drug degradation is quite probable at the higher temperature because the release of the water of hydration from the monohydrate form can affect moisture-sensitive drugs.

Bile Acids, Sterols, and Steryl Esters: Many of these compounds have high melting points, making them unsuitable for melt applications. Exceptions are the salicylic acid–cholic acid system formed by a melt-granulation technique reported by Froemming and

Vetter (10). The system provided a sustained release in acid media (pH 1–3.5).

Sugars: Again, many sugars have excessive melting points to be considered viable candidates for melt-congealing processes. However, the use of a few of the sugars has been reported in the literature. The application of zylitol in the formulation of the diuretic hydrochlorothiazide was demonstrated by Sirenius and coworkers (11). Hirasawa et al. (12) prepared naproxen solid dispersions by melting and rapid cooling with liquid nitrogen, using lactose as a carrier. Danjo and associates (13) prepared ethenzamide solid dispersions using sugars such as sucrose, maltose, galactose, and mannitol as carriers by melting and rapid cooling with liquid nitrogen. It was found that solid dispersions made with amorphous sucrose were more stable than those made with other sugars.

Urea: Urea has been used both to form solid dispersions by the cooling of urea–drug mixtures and to directly coat drug-laden particles in melt-coating operations. It has a melting point of approximately 130°C and is highly soluble in water. A variety of urea–drug dispersions obtained from melt processes have been reported in the literature, and these include aspirin, paracetamol, phenobarbitone, and tolbutamide. One disadvantage of using molten urea is its instability, resulting in the evolution of ammonia.

Polyethylene Glycols (*PEG*): These represent one of the most common materials used in the formation of solid dispersions from melts. The family of PEG polymers has molecular weights ranging from a few hundred to a few hundred thousand. Typical values for solid dispersions are 2000–20,000. Examples of solid dispersions of griseofulvin, indomethacin, and tolbutamide in PEG formed by the coagulation of PEG–drug melts have been reported extensively in the literature. PEG has the added advantage of increasing the water solubility of many drugs. This, along with its availability in many molecular-weight forms, makes it a popular material for the formation of solid dispersions.

Poly (*Ethylene Oxide*) (*PEO*) *Polymers*: In the same family as PEG, but having higher molecular weights are POLYOX® resins, which are water-soluble polymers. Because of their low melting point and unique swelling properties, coupled with the controlled rate of dissolution, POLYOX resins have been used to make sustained-release formulations by hot-melt extrusion (14).

Hydroxypropyl Methylcellulose (*HPMC*): Suzuki and Sunada (15a, 15b) report the production of solid dispersions prepared with nicotinamide and HPMC as combined carriers using nifedipine and nitrendipine as model drugs. Their solid dispersions were obtained using the fusion method. After both the drug and HPMC were dissolved in the liquid melt of nicotinamide at 140°C, the fused mixture was cooled to solidify it.

Natural and Synthetic Waxes: The most common natural wax used as a congealing agent is carnauba wax derived from the wax palm or carnauba (*Copernicia cerifera*) found in Brazil. The major constituents of this wax are aliphatic esters, hydroxy esters, and methoxycinnamic and hydroxycinnamic aliphatic diesters. This is one of the hardest and highest-melting-point natural waxes (m.p. 82–85°C). It is used both as a coating agent, (9, 16) and as solid dispersion carrier (4, 17). Other natural waxes used in congealing applications include paraffin waxes and beeswax (18, 19). Synthetic waxes, such as stearic acid and stearyl alcohol, are often used in the formulation of sustained-release wax matrices by melt-congealing processes (20).

Hydrogenated Vegetable Oils: These primarily consist of the family of stearines. Hydrogenated castor oil (Cutina HR®) has been used as a wax matrix material both in melt-granulation (21) and spray-congealing processes (22).

Glycerides and Polyglycolyzed Glycerides: Most common carriers used in the preparation of sustained-release wax matrix formulations are glycerides and polyglycolyzed glycerides. There are several commercial products on the market, for example, Compritol 888 ATO (glyceryl behenate), Myverol 18092 (distilled monolinoleate), Myverol 18-99 (distilled monooleate), and Myveplex 600 (glycerol monostearate). They have been used as hydrophobic coatings (19), spray-congealing agents (11, 23), and retardant materials to form wax matrices (24).

Other Polymers and Excipients: Some other excipients have been used in the preparations of solid dispersions and sustained-release wax matrices by melt-congealing processes. The most common examples are the family of ethylacrylate and methylmethacrylate copolymers (Eudragits). Although these agents are generally not suitable for melt formation, they have been used successfully to modify the release of products formed by melt processes. For example, Miyagawa et al. (25) used both hydropropylcellulose and Eudragit L-100 to modify the release characteristics of diclofenac sodium from granules formed by the melt extrusion of a mixture of drug, release agents, and carnauba wax. The application of these excipients has also been demonstrated by Emori and colleagues (26).

IMPORTANT PROCESSES AND EQUIPMENT

Coating Processes

When the active ingredient is contained in an inert core material, for example, granulated with sucrose, and a

sustained-release coating of a congealable material is desired, then the equipment of choice is often the fluidized bed using a top-spray configuration (27). However, a bottom-spray configuration using a Wurster column insert can also be used. The fluidized bed offers the unique advantage of very high rates of heat and mass transfer from the molten solid to the particles to be encapsulated. Important processing variables are the temperature of the bed, temperature and flow rate of fluidizing air, temperature of the molten material and atomizing air; spray rate; and atomizing air pressure. According to Jones and Percel (28), the product temperature and droplet size of the molten material being sprayed (this is a function of atomization air pressure and spray rate) are the key variables. Special attention must also be given to the insulation of the spray nozzle within the bed to avoid remelting coated particles that come in contact with the nozzle during processing (9). The heat tracing of the lines containing the molten material is also imperative to avoid the solidification of coating material before reaching the nozzle. Jozwiakowski et al. (27) investigated the coating of a sugar-based granulation with a partially hydrogenated cottonseed oil (Durkee 07 Stearine, Durkee Industrial Foods) using a factorial experimental design. The melting point of this wax was 64°C, and it was found that excessive growth and rough coated surfaces were obtained when the bed temperature was held at 58°C. However, particles coated at bed temperatures of 54 and 50°C had uniform, smooth coated surfaces.

A novel fluidized-bed coating application that avoids the use of a spray nozzle for the delivery of the congealable solid additive was demonstrated by Kennedy and Niebergall (18, 19). They coated chlorpheniramine maleate (CPM)-loaded nonpareils with a variety of different waxes, including beeswax. The method of preparation involved loading a fluidized bed with both the nonpareils and the coating agent, both in powder form. The bed was then fluidized with heated air, the temperature of which was varied. The process consisted of four steps: 1) equipment warm-up, 2) preheating of substrate, 3) melting and spreading of the coating agent, and 4) cooling and subsequent solidification of the coating agent. Dissolution-release profiles for the nonpareils coated with beeswax showed significant sustained-release characteristics. The coating of nonpareils from 10 to 35 mesh and particles up to 1 g are reported to be feasible.

Spray-Congealing Processes

The formation of drug dispersions within a congealed matrix is conveniently carried out in a spray-congealing apparatus. The process and important operating parameters for this type of equipment are addressed in detail by Killeen (29). The basic steps in the spray-congealing process are described in Fig. 4. First, the molten liquid, containing all the excipients, is fed to an atomizing nozzle. The atomized droplets then leave the nozzle and enter the cooling vessel or chamber, where they mix with chilled air. The droplets solidify and either fall to the bottom of the chamber or become entrained in the upward-moving airflow. The smaller particles that become entrained in the flow of air are separated from the air in a cyclone separator. The larger particles that settle to the bottom of the chamber are discharged. If necessary, the product can be size-separated as needed before further processing.

The atomizing nozzle may be one of four basic types: 1) dual-fluid, 2) single-fluid pressurized, 3) single-fluid disk or rotary, and 4) single-fluid ultrasonic. As with all congealing processes, the feed lines must be heat-traced to avoid unwanted solidification, and the nozzle should be insulated within the equipment to avoid the remelting of product coming in contact with it. For the best control of particle size and uniformity, the dual fluid or atomizing air nozzle is recommended. This nozzle can produce particles well below 50 μm, and because the airflow rate and pressure can be controlled separately, the size of the droplets can be controlled independently of the liquid flow rate. The air atomizing nozzles become problematic when the viscosity of the molten liquid is very high or the amount of solids loading in the melt is high. In these cases, the single-fluid nozzles are often preferred. Single-fluid pressurized (hydraulic) nozzles make use of the pressure of the fluid to cause atomization when flowing through the small orifice holes in the nozzle. These devices are suitable when the solids content of the melt is low and droplet size

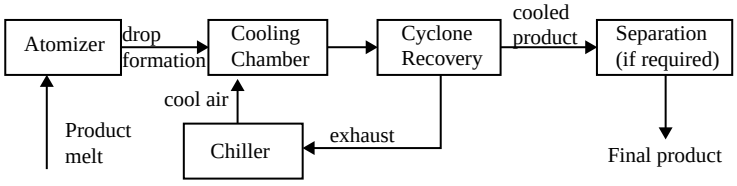

Fig. 4 Subprocesses occurring during spray congealing. (From Ref. 29.)

is not too small (for example, not less than 100–200 μm). Disk or rotary atomizers consist of a disk connected to a rotating shaft onto which the molten liquid flows. The liquid is broken up into drops by the spinning motion of the disk that produces a thin, radial outward-moving droplet spray pattern. This gives rise to a collection chamber that is short and wide, which requires less headroom than for processes using hydraulic and air atomized nozzles. The size distribution of the product is controlled by the liquid feed rate and the speed of rotation of the disk. These types of nozzle can process molten liquids that are corrosive, heat-sensitive, and contain less than 20% solids. In processes that use either hydraulic or rotary nozzles, the rate of cooling of the drops is relatively slow, and the flow of cocurrent and/or countercurrent air in the cooling chamber is significantly greater than for air atomizing nozzle systems. The use of ultrasonic nozzles for the manufacture of congealed solid products is relatively new. This type of nozzle uses the movement of an oscillating plate vibrating at ultrasonic frequencies to break up a liquid stream fed to the surface of the plate. The droplets formed are generally very small (less than 30 μm) and are suitable for low liquid flow rates. Because the droplet formation process imparts little directed kinetic energy to the drops, the spray pattern is quite small and controlled. In a recent study, Rodriguez and associates (22) demonstrated the efficacy of using an ultrasonic nozzle to produce spray-congealed products of theophylline and fenbufen in wax matrices.

The cooling chamber design must allow for the disengagement of the solidified droplets from the cooling air stream while also allowing the droplets sufficient residence time to cool and solidify. For a given liquid feed rate and composition, the amount of cooling is fixed. This is because the heat removal is equal to the latent heat of solidification plus the sensible heat of cooling the product, both of which are fixed by the liquid feed rate. The finer the droplets that are produced, the slower the air velocity must be to allow for disengagement; however, heat transfer tends to be rapid for small drops. Therefore, because the flow of air is essentially fixed owing to the cooling duty, this leads to wider and shorter cooling vessels. For larger droplets, particle disengagement can take place at higher gas velocities. However, heat transfer is slower, and droplet residence time must be longer. This leads to narrower and taller cooling vessels. Countercurrent and cocurrent airflows are possible as are mixed airflow patterns; several other design considerations are discussed by Killeen (29). Other important product parameters such as molten liquid viscosity, surface tension, specific gravity, and solids concentration, and processing parameters such as air flow rate, flow patterns, spray angle, spray impingement, and nozzle resistance to abrasion are also addressed in this reference. According to Yajima et al. (30), the key product variable for the successful production of a wax matrix containing clarithromycin that masked the bitter taste of this macloride antibiotic was the congealing speed. The important process variables were the liquid feed rate and atomizer (rotary) wheel speed.

Granulation Processes

The mixing of drug powder into a wax matrix and the subsequent uniform dispersion of the drug within the matrix can be carried out using a variety of granulating techniques. Thies and Kleinebudde (31) describe a process by which a hygroscopic drug, sodium valproate, was dispersed in a meltable binder, glycerol monostearate, using a high-shear mixer. The high-shear mixer was modified by adding a temperature bath that surrounded the mixing bowl. The prescreened drug was first added to the bowl and preheated and mixed for 10 min. The binder (glycerol monostearate) was then added to the mixer, and the granulation process began. Because of the hygroscopic nature of the drug, all formulation-related activities were performed in atmospheres with a relative humidity of less than 40%. The solidification temperature of the drug–binder combination was approximately 35°C. This temperature was approximately 35°C lower than the pure binder owing to the addition of the drug. The resulting granules, in the size range of 4 mm–500 μm, were cooled to room temperature and used for analysis. The effects of several process variables on the properties of the granules were investigated. These variables included the amount of binder, the process temperature, the granulation (massing) time, and the speed of the impeller.

Evrard et al. (21) investigated the influence of the melting and rheological properties of the binder in high-shear mixer granulation processes. These researchers concluded that successful granule formation took place in high-shear mixers using a variety of low-melting-point binders (Compritol® 888, Cutina® HR, and Precirol® ATO5) at temperatures below their melting points. The binder only needed to be softened to produce granules. The melting range of the binder and the effect of temperature on the binder viscosity influenced the rate at which granules grew during the particle-formation process.

Melt-Extrusion Processes

The hot-melt-extrusion process is a well-established unit operation in the polymer pelleting and compounding

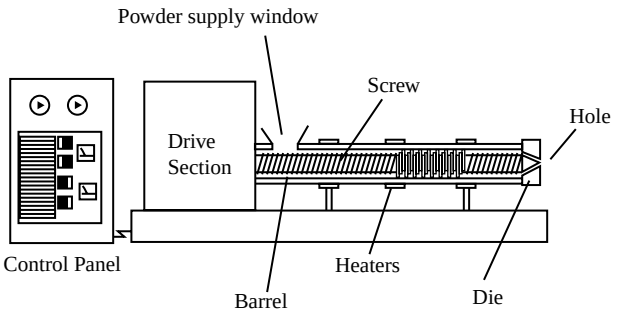

Fig. 5 Schematic diagram of a twin-screw compounding extruder. (From Ref. 25.)

industry. The concept is to feed a polymer powder along with desired additives, such as fillers, dyes, and other polymers, and then subject them to a high temperature and very high-shear environment. The temperature causes the polymers to melt, and the high shearing action of the screw(s) causes the other additives to be intimately mixed and dispersed within the polymer melt. Both single-screw and twin-screw units are common; the latter is capable of producing much higher pressures than is the single-screw unit. A schematic diagram of a twin-screw extruder is shown in Fig. 5. The extruder consists of essentially seven regions: the powder supply window, the barrel, the screws, the die, the drive section, the cooling/heating unit, and the control panel.

Because the process of polymer-compounding is very similar to the dispersion of a drug in a congealable solid matrix, it is not surprising that hot-melt extrusion techniques have been applied to the production of wax matrix formulations. Miyagawa et al. (25) used a twin-screw compounding extruder to prepare granules of diclofenac sodium dispersed in a carnauba wax matrix. They cited the following advantages of using such a device:

- High kneading and dispersing ability can be achieved within the unit independently of the physical and chemical properties of the excipients.
- The temperature in each zone of the unit can be controlled accurately.
- The unit demonstrates superior extruding capability.
- Residence time of powders in the barrel is minimized, thus minimizing the product degradation.
- The unit is easy to clean.

Zhang and McGinity (14) also demonstrated the use of this type of equipment to formulate a sustained-release tablet of chlorpheniramine maleate (CPM) dispersed in a wax matrix consisting of polyethylene oxide (PEO). The content uniformity of their extruded tablets was in the range of 99–101% of theoretical drug content, which for a low-dose drug such as CPM was considered very good. For this application, the sustained-release profiles were significantly affected by the addition of polyethylene glycol (PEG). The release rates increased with increasing amounts of PEG. PEG was also found to significantly lower the required processing temperature and reduce the required torque needed to extrude the tablets. These investigators concluded that the hot-melt-extrusion process was suitable for the preparation of these sustained-release tablets and that significant drug degradation, caused by the relatively high processing temperatures, was avoided because of the short residence time of the drug in the barrel (2–3 min).

IMPORTANT APPLICATIONS

Sustained-Release Dosage Forms Made Using Melt-Congealing Processes

Many prolonged- or sustained-release dosage forms are made using melt-congealing processes. The dosage forms can be melt-congealed matrix granules in the form of capsules or compressed into tablets or melt-congealed coatings on drug-loaded substrates (particles or pellets in capsules). Wax matrices are often prepared by melt-granulation or melt-extrusion processes, whereas microspheres or microparticles are usually produced by spray-congealing processes, and coated particles or pellets can be made by hot melt-coating processes.

The formation of drug containing wax-coated microspheres can be considered a coating process, although it is more correct to describe it as an encapsulation process involving a phase-inversion technique. Giannola et al. (16) demonstrated this technique by producing carnauba wax microspheres loaded with valproic acid (VA). These microspheres were between 200 and 425 μm in diameter, with an average drug content of 26% w/w. The process used to manufacture this product consisted of melting carnauba wax in an oil bath at 110°C and then adding a sample of the VA. To this homogeneous melt was added an acidic aqueous solution (pH 4.5), which minimized the solubility of the VA, combined with glycerine, which increased the melting point. A small amount of surfactant (Tween or Spans®) was added, and then the mixture was stirred at a predetermined rate. On dispersion in the aqueous medium, the molten mass formed spherical particles. The mixture was then quenched by the addition of iced water, with the result that the carnauba wax solidified and enveloped the drug.

Miyagawa and coworkers (25) used a twin-screw extruder to prepare wax matrix granules (WMG)

consisting of diclofenac sodium (DS) as a model drug; carnauba wax as the matrix material; and hydroxypropylcellulose (HPC–SL), methacrylic acid and copolymer L (Eudragit L-100), and sodium chloride as rate-controlling agents. The dissolution behavior of DS from WMG was strongly influenced by granule formulation. The release rate can be manipulated by the addition of other rate-controlling agents.

Emori et al. (26) formulated wax matrix tablets for prolonged drug release using a melt-congealing process. They studied the addition of acrylic acid polymer on the release of drug from a wax matrix consisting of carnauba wax and stearyl alcohol in a 1:1 ratio.

Perez and colleagues (24) prepared sustained-release phenypropanolamine HCl tablets and investigated the effects of varying wax levels and methods of matrix formulation on drug release. Two methods were used for the preparation of a drug–wax system: physical mixtures and solid dispersions. In the first method, the drug, wax, and diluent were blended in a Turbula mixer by geometric dilution for a total of 20 min. Then the mixture was compressed into tablets. For the solid-dispersion method, the wax was melted in a water bath at a temperature of 80–85°C. The drug was incorporated into the melted wax using constant stirring over a 5-min period, and then the mixture was allowed to cool until it solidified. The solidified mass was granulated using a Stokes oscillating granulator equipped with a no. 12 screen. Blending of milled material (wax and active ingredient) and diluent was done in the Turbula mixer for 20 min. The tablets that were prepared as a physical mixture gave higher drug release than did tablets prepared by the solid-dispersion process.

The formation of a barrier coat on drug-laden substrates, to protect the drug from gastric fluid or to provide sustained release of the drug, can be achieved by the hot-melt fluid-bed coating process. Processing conditions must be chosen to prevent solidification of the coating material in the feed lines and to obtain smooth, uniform coats without excessive spray-drying and agglomeration. Kennedy and Niebergal (19) coated chlorpheniramine maleate (CPM)-loaded nonpareils with hydrophobic coating agents such as beeswax, paraffin, etc. in a hot-melt fluid-bed coating process. They demonstrated the ability to extend the release profile of a highly water-soluble drug, CPM.

Solid Dispersions for Improving the Solubility of Poorly Water-Soluble Drugs

As previously noted, the use of solid dispersions to improve the solubility of poorly water-soluble drugs dates back to 1961 (1). Pharmaceutical composition with good dissolution and bioavailability can be formulated from solid dispersions of pharmaceutically active ingredients. Solid dispersions also can be used in controlled-release formulations.

The principle of improving the solubility of poorly water-soluble drugs using solid dispersions has already been presented. One common method of preparing solid dispersions is melt-congealing. The carriers used to make solid dispersions of poorly water-soluble drugs have also been addressed.

Dispersions of drugs in matrices can be formed either by dissolution of the drug in a molten solid and subsequent solidification or by the mechanical dispersion of the drug in a molten liquid followed by solidification. If the drug is poorly water soluble, then the matrix material should be either highly water soluble or highly water permeable. The equipment used for the preparation of drug dispersions is quite varied and includes spray congealers, granulators, and melt extruders.

Nifedipine is a poorly water-soluble drug, and much research has been conducted to improve its solubility. Suzuki and Sunada (15a) prepared solid dispersions of nifedipine in a combined carrier of nicotinamide and hydroxypropyl methylcellulose (HPMC). The nicotinamide was melted at 140°C, and then the drug and HPMC were added into the melt and dissolved. The melt mixtures were cooled and solidified to form the nifedipine solid dispersions. The solubility of the drug in the solid dispersion was enhanced. The drug dissolution of this ternary dispersion system was influenced by the viscosity and weight fraction of HPMC, the solubility and weight fraction of the drug, and the humidity during storage.

Suzuki and Sunada (15b) also prepared solid dispersions of nifedipine with other combined carriers using a fusion (melt) method. The combined carriers were nicotinamide and four different water-soluble polymers: hydroypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), partially hydrolyzed polyvinyl alcohol (PVA), and pullulan. HPMC, PVP, and PVA dissolved in the melt of nicotinamide and were effective in the amorphous formation of nifedipine in solid dispersions. In dissolution studies, the drug concentration for these dispersions increased to more than twice the intrinsic drug solubility.

Hirasawa and coworkers (12) prepared a naproxen solid dispersion by melting, followed by rapid cooling with liquid nitrogen using lactose as a carrier. The dissolution studies of naproxen indicated that the dissolution rate was markedly increased in solid dispersions compared with physical mixtures and pure drugs.

Doshi et al. (32) prepared solid dispersions of carbamazepine in polyethylene glycols (PEG), PEG 4000

and PEG 6000, by both the melt and solvent methods. A comparison of dissolution profiles of the solid dispersions indicated dramatic increases in the rate and extent of carbamazepine dissolution from the solid dispersions. The melt (congealing) method provided a significantly higher rate and extent of dissolution of carbamazepine than did the solvent method. In addition, the rate and extent of dissolution of carbamazepine were significantly greater when the solid dispersion was cooled (slowly) at room temperature compared with faster cooling with ice.

Van den Mooter et al. (33) prepared solid dispersions of tamazepam in PEG 6000 and polyvinylpyrrolidone K30 (PVP K30) by the fusion (melting) and cooling process. In contrast to the very slow dissolution rate of pure temazepam, the dispersion of the drug in the polymers enhanced the dissolution rate considerably. This can be attributed to improved wettability and dispersibility and a decrease of the crystalline fraction of the drug.

Taste-Masking and Prevention of Environment Degradation

Yajima et al. (30) applied the spray-congealing technique to mask the bitter taste of clarithromycin, a macloride antibiotic. An optimum wax matrix formulation was developed consisting of 30% clarithromycin (CAM), 60% glyceryl monostearate (GM), and 10% aminoalkyl methacrylate copolymer E (AMCE). The CAM wax matrix was made by a spray-congealing agglomeration process. AMCE was dissolved in melted GM at 12°C. CAM was added to the melt and homogeneously suspended. Subsequently, the suspension was transferred to a spray-dryer and atomized under various atomizer wheel speeds and liquid feed rates. It was found that a small spherical matrix with a smooth surface could be obtained with a high atomizer wheel speed and optimum liquid feed rate. This matrix also possessed excellent properties for taste-masking with small initial amounts of release and subsequent high rates of release.

The masking of unpleasant taste and the prevention of environmental degradation of the drug can also be achieved by applying a barrier coating in a melt-congealing process.

THE STABILITY AND STRUCTURE OF THE CONGEALED MATERIAL

Analytical Techniques

Differential scanning calorimetry (DSC), x-ray diffraction (XRD), and infrared spectroscopy are the common techniques used in the characterization of the structure of the congealed solid. Thermal analytic methods, such as DSC and differential microcalorimetric analysis (DMA), are routinely used to determine the effect of solutes, solvents, and other additives on the thermomechanical properties of polymers such as glass transition temperature (Tg) and melting point. The x-ray diffraction method is used to detect the crystalline structure of solids. The infrared technique is powerful in detecting interactions, such as complexation, reaction, and hydrogen bonding, in both the solid and solution states.

Case Studies

Numerous studies have been reported in the literature that investigate the micro- and macrostructure of the congealed solid and its affect on the dissolution of the active ingredient. The structure of the solid phase formed on congealing is affected by the process by which the material is congealed, the formulation, and the conditions at which the solid product is stored.

Zhang et al. (14) produced matrix tablets containing chloropheniramine maleate (CPM) dispersed in mixtures of polyethylene oxide (PEO) and polyethylene glycol (PEG) using melt-extrusion. Physical characterization of the samples was performed using differential scanning calorimetry (DSC), wide-angle x-ray diffraction (WAXD), infrared spectroscopy, and gel permeation chromatography. Results showed that the PEO and PEG consisted of ordered crystal regions interdispersed in random amorphous regions. WAXD verified that crystals of CPM and PEO existed in the matrix tablets. The effect of PEG was to lower the processing temperature and also the required torque necessary to extrude the melt through the die. This, in turn, had the effect of reducing damage to the polymer (and drug) during tablet formation. Polymer damage was primarily attributed to the intense shear force occurring during extrusion. This caused bond breakage and a reduction in molecular weight. The introduction of PEG caused a significant reduction in the melt viscosity and thus allowed a reduction in the processing temperature. An increase in the ratio of PEG to PEO also caused an increase in the rate of drug release during in vitro dissolution tests.

Emas and Nyqist (17) investigated the aging and stabilization of spray-congealed solid dispersions of carnauba wax. Isothermal microcalorimetry (IM) was used to measure the behavior of samples of freshly congealed wax and samples stored for 2 days at elevated temperatures of 40, 50, and 60°C, respectively. Results for the freshly obtained sample and the annealed samples are illustrated in Fig. 6, where the rate of change of heat content (dq/dt) is plotted as a function of testing time.

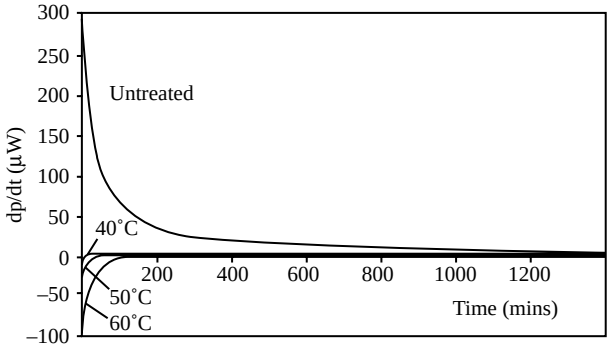

Fig. 6 Results of microcalorimetric measurements of spray-congealed carnauba wax. Untreated sample and samples annealed at different temperatures and stored for 5 days at ambient conditions; all measurements taken at 45°C. (From Ref. 17.)

Exothermic reactions are represented by positive deviations, whereas endothermic reactions are represented by negative deviations. From this figure, it can be clearly seen that the effect of annealing the samples at different temperatures is to reduce the magnitude of the exothermic reaction. The absolute values of the deviations depend on the temperature at which the experiments are run. However, the trend of reduced exotherms with increasing annealing temperature is followed for all temperatures. A series of experiments was also performed to evaluate the effect of long-term storage on the rate of change of heat content with time. Again, the results depend on the testing temperature, but the trends are similar. Fig. 7 illustrates the results for a wax sample annealed at 50°C for 2 days and then sealed and stored at room temperature for up to 12 months. From this figure, it can be seen that the initial

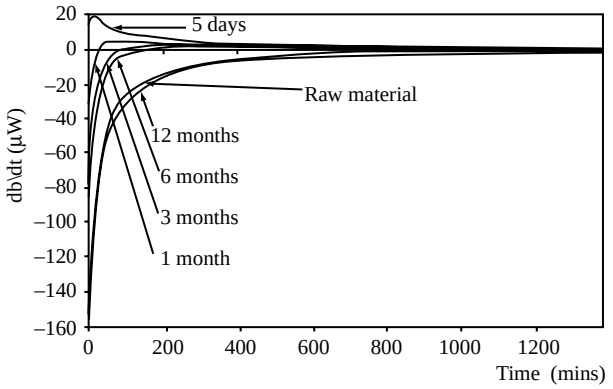

Fig. 7 Results of microcalorimetric measurements of spray-congealed carnauba wax. Samples annealed at 50°C for 2 days and stored for various times at ambient conditions all measurements taken at 45°C. (From Ref. 17.)

exothermic reaction is reduced in magnitude with increased storage temperature and that a stable condition (similar to that obtained for the raw wax) is approached asymptotically with time. From this work, it can be seen that spray-congealed carnauba wax initially exists in an unstable form that slowly changes to a stable form on storage (aging). This aging process can be accelerated by annealing the samples at an elevated temperature (40–60°C) for several days before storage. However, the rate of aging is a complex function of the annealing history because the wax appears to have different stable states at different temperatures.

Eldem et al. (34) investigated the polymorphic behavior of congealed micropellets of two different drugs (estradiol cypionate and medroxyprogesterone acetate) in two lipids, GTS-33 (glycerol tristearate) and Compritol 888 (glycerol behenate). Micropellets were formed from the drug and congealable matrix (tristearate–behenate), and then separate samples were taken, sealed, and stored for 6 months at temperatures of −18, 4, 25, and 37°C, respectively. DSC was used to investigate the stability of the samples after the storage period, and scanning electron microscopy (SEM) was used to measure the surface morphology of the microspheres. It was concluded that all the samples initially possessed an unstable polymorphic structure with a smooth surface morphology corresponding to the α-form, which is the result of rapid crystallization from the melt. According to Garti and Sato (35), the α-form possesses a very small crystal size accounting for the smooth surface morphology. The rate of attainment of the more stable β-form is dependent on the storage temperature. The presence of additives, such as lechtin, can also significantly affect the rate of change of crystalline structure. Higher storage temperatures increase the rate of polymorphic transformation, whereas the addition of lechtin acts as a stabilizer, slowing this transition.

McGinity et al. (36) investigated how the cooling process influenced the properties of solid dispersions prepared by congealing mixtures of drug and wax matrix. The system that was studied was tolbutamide in urea and in PEG (6000). Powder x-ray diffraction was used to determine the extent of crystallinity of these solid dispersions. For the tolbutamide–urea system, rapid cooling of the melt gave rise to distinct crystalline forms of the drug and wax. However, slow cooling of the melt in an oil bath at ambient conditions over a period of several hours yielded a solid that exhibited a complete absence of crystallinity. This amorphous solid did yield a crystalline structure after 5 months of storage, but the crystals were those of urea only. This is in contrast to simple physical mixtures of the two solids that clearly

showed crystalline mixtures of both tolbutamide and urea. In contrast to the tolbutamide–urea system, the tolbutamide–PEG system showed similar degrees of crystallinity for both the rapid-cooled and slow-cooled systems. Dissolution profiles for this system were compared for the rapid-cooled, slow-cooled, and physical mixture samples. The profiles for all three samples were very similar; however, the extent of release from the rapid-cooled sample was approximately 10% higher than that of the other two samples at any given time during the dissolution process.

Coben and Lordi (37) investigated the hardening of a variety of suppositories using a modified Krowczynski (38, 39) apparatus. The suppository bases were commercially available materials that consisted of a mixture of natural and synthetic waxes and fats. Samples were prepared from the different base materials by coagulating melted materials in 50-cavity brass molds. The samples were allowed to set at different storage temperatures (−5, 4, and 22°C), and this resulted in molding times of approximately 5, 15, and 30 min, respectively. After molding, samples from each batch were stored at three different temperatures of 4, 20, and 30°C, respectively. Both DSC and XRD were used to evaluate crystalline and polymorphic changes in the suppository base material. The results clearly indicated that the age-hardening phenomenon was solely attributable to a shift from an amorphous to crystalline structure and that polymorphic changes did not occur. Results also showed that the times required to resoften the samples at a given condition were dependent on the storage temperature but did not depend on the rate of solidification during the molding process.

From the case studies presented here, it is clear that the structural changes in the congealed material vary considerably and that it is difficult to identify and generalize these trends for a family of excipients. Nevertheless, it is fair to say that aging effects are common to many congealed materials and that carefully planned experimental studies must be conducted to evaluate the different phenomena causing these changes.

ADVANTAGES AND DISADVANTAGES

The advantages of using melt-congealing processes are numerous. Generally, no solvent is required in the formulation and manufacturing processes, and the subsequent environmental requirement of solvent capture and recycle is eliminated. Processing times are often much shorter because solvent evaporation is not required. For example, in coating processes, the time to congeal a molten liquid is much shorter than that required to evaporate a solvent. In addition, undesirable drug–solvent interactions are also eliminated. For example, drugs that are highly water labile can be processed using melt processes.

There are also disadvantages to using melt-congealing processes. The drug must be stable at the temperature required to melt the carrier. For many drugs, the temperature at which degradation takes place is low and may preclude the use of all suitable matrix materials. Processing using hot-melt flows requires careful engineering to avoid feed-line solidification and unwanted agglomeration. Many of the matrix materials used to form dispersions and coatings undergo aging during storage, and this can affect the stability of the drug and/or the release rate of the drug.

SUMMARY

There are many applications of melt-congealing techniques in controlled-release dosage forms, improving the solubility of poorly water-soluble drugs and taste-masking of bitter drugs. Although the incorporation of an active ingredient into solid dispersions is a good way to enhance the solubility of poorly water-soluble drugs, the stability and aging problems associated with the congealed solids still need extensive additional study.

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